Master's Degree Dissertation

Cost-effectiveness and cost-utility analysis of Deprexis®, a digital therapy intended for the treatment of mild to severe depression, in Catalonia

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Abstract

Depression is an illness that has a strong social and economic impact, and that has seen its prevalence increased during the COVID-19 pandemic. As with many sectors of healthcare, the increased costs of treatment and the scarce availability of professionals lead to long waiting lists, generating a need for digital innovation in the management of depression. Deprexis® is a digital therapy that has been recently approved for its reimbursement under prescription in Germany and that has been studied for its efficacy in the treatment of depression as a complement of care-as-usual, as a partial replacement of care-as-usual (CAU) and as a tool to be used in patients in waiting list. In this study the incremental cost-effectiveness ratio (ICER) and incremental cost-utility ratios (ICUR) of the introduction of Deprexis® as a complement of CAU for the treatment of depression in the region of Catalonia and from the perspective of both, society, and that of the National Health Service, were estimated using a Markov model. It was found that, when compared with CAU, the introduction of Deprexis® incurred an ICER of 3,866 € per clinically improved individual over a one-year time horizon and a ICUR of 125,498 € per quality-adjusted life year from the perspective of the National Health service, and 2,248 € per clinically improved individual and 72,970 € per QALY from the societal perspective.

Keywords: cost-effectiveness; cost-utility; COVID-19; depression; digital health; Markov model

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1. Introduction and motivation

The main motivation for this study is the growing trend in digital therapeutics in the healthcare sector, amplified during the COVID-19 pandemic, and the evolving legal environment that regulates their price and reimbursement (1). In 2019, Germany adopted the Digital Healthcare Act (DiGA), a regulation that outlines the eligibility criteria for the reimbursement of prescribed digital therapies (mobile apps or web platforms)(2). Under this act, digital therapy manufactures must present evidence, cost-effectiveness and budget impact analyses, to negotiate a reimbursement price with the Central Federal Association of the Health Insurance Funds (3,4). Furthermore, with this act, Germany has paved the way for other administrations to follow, meaning that digital therapy manufacturers will have to consider the inclusion of the endpoints necessary for the economic evaluation of their products from at an early stage of clinical development.

To exemplify the economic evaluation of a digital therapy, Deprexis® was chosen as the study's intervention. Deprexis® is a digital therapy indicated for the treatment of unipolar depression or depressive disorders as a supplement of care-as-usual (CAU) in adults (5). Deprexis® was chosen as the study's intervention mainly since it was the 11th digital therapy approved for reimbursement under the DiGA (6) and several papers were published on its extensive clinical development that provided substantial evidence on its efficacy(5,7).

Another reason for choosing Deprexis® for the study was that it is intended for the treatment of depression, a highly prevalent mental illness that is characterized by a high relapse rate(8,9). Depression has become an even larger issue since the COVID-19 pandemic, it has been observed that the lockdown and isolation have increased its prevalence by up to seven times (10), prior to the pandemic, depression was present in approximately 5% of adults worldwide and 5.7% of adults in Spain (8,11).

Furthermore, depression is a leading cause of disability worldwide and it is a major contributor to the overall global burden of disease. The most common symptoms of depression are pain, fatigue, weakness, poor concentration, feelings of excessive guilt or low self-worth, hopelessness, thoughts about dying or suicide, disrupted sleep, and changes in appetite or weight (8). In the Study on the Costs and Burden of Depression in Catalonia, it was estimated that, in 2006, depression had a cost of 152 million euros for the regional health service, approximately 1.9% of the public health budget of Catalonia. From the perspective of society, which included the costs of loss of productivity and premature death, the cost of depression ascended to 580 million euros (12).

Depending on the severity of the disorder, the treatment of depression may include psychological treatment, particularly cognitive behavioural therapy (CBT), and/or antidepressant medication (8). In Spain, the access to psychotherapy is limited, as there are only 20 psychologist per 100,000 inhabitants which translates into waiting periods that can range from 26 to over 70 days and, in many cases, results in the patient opting for private practice (increased societal cost)(11). Also, psychotherapy has an elevated cost, approximately 75 € per hour of session in Catalonia (12). It is therefore evident, as with the entire healthcare sector, that there is a need for digital innovation in the management of depression. Deprexis® is a clear example of digitalization in this area, as in its clinical development it has not only been studied as a complement of CAU, but also as a technology that could partially replace face-to-face CBT or versus the CBT waiting list (7).

Deprexis® is an interactive online platform that delivers CBT techniques in ten modules (5):

- **Behavioral activation**: the relationship between activities and depression.
- **Cognitive modification**: reviews the impact of unwanted thoughts and behaviors, and how to overcome these patterns.
- **Relaxation, physical exercise, and lifestyle modification**: relaxation exercises to cope with stress and reduce tension.
- **Acceptance and mindfulness**: the effects of suppressing thoughts and other emotional control efforts.
- **Problem solving**: developing a structured approach to overcoming challenges.
- **Childhood experiences**: How early childhood experiences contribute to vulnerability and depression.
- **Interpersonal skills**: the relationship between social relationships and depression.
- **Positive psychology**: exploring different strategies to foster well-being and happiness.
- **Dream work and emotion-focused interventions**: dreams as a way to improve daily problem solving.
- **Psychoeducation**: information on depression.

The modules are presented to the patient in a sequence that is tailored to their needs. The program provides information on the subject, generates questions and proposes answers. Subsequently, the program selects material to match the responses, in what is described as a ‘simulated dialogue’ to tailor the content to the user. The program is mainly based on text dialogue, however, it also includes audio, photographs, drawings , worksheets and summary sheets (5,7).

The objective of this study was to estimate the incremental cost-effectiveness (ICER) and cost-utility (ICUR) ratios of the introduction of Deprexis® as a complement of CAU in the treatment of depression in the region of Catalonia from the perspective of both, society, and that of the National Health Service (NHS).

2. Methods

The present economic evaluation was performed in accordance with the Guideline for the Economic Evaluation of Health Technologies by López Bastida et al. (13). To calculate the ICER and ICUR of the introduction of Deprexis® as a complement of CAU for the treatment of depression in the region of Catalonia, a Markov model was developed on Excel to simulate the progression of the patients through different health states and capture their costs and health impacts.

2.1. Markov model's characteristics and structure

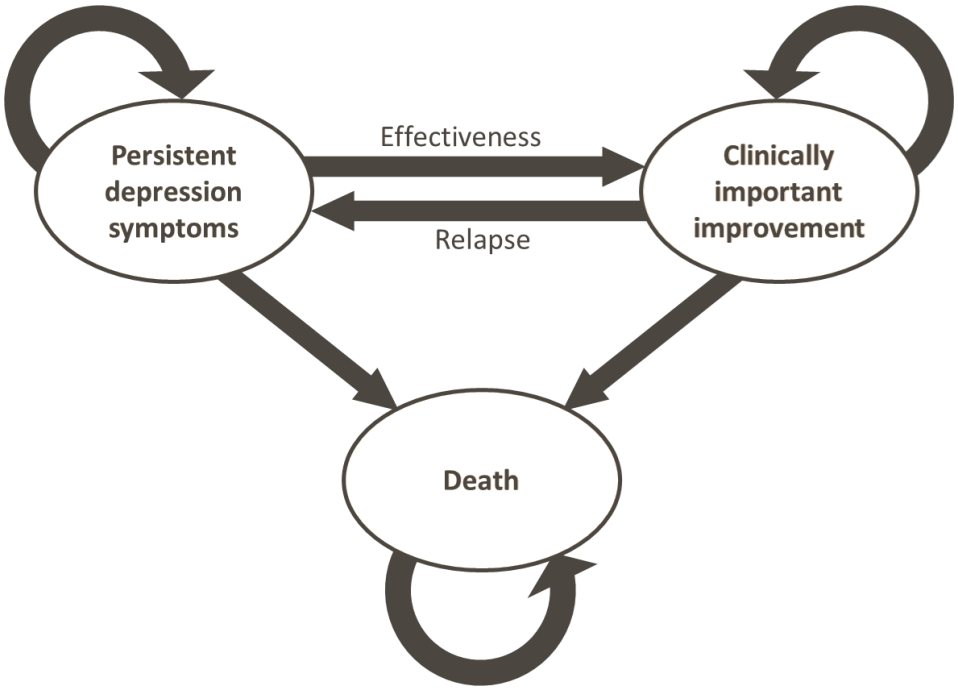
The intervention chosen for this study was Deprexis® as a complement of CAU, which includes any form of treatment, such as antidepressant medication and psychotherapy, and the comparator was CAU by itself (14). The model was structured into 3-month cycles, to align with the endpoints of the clinical development, for a time horizon of 1 year. Furthermore, a 3% discount rate was applied (13) for both, the effectiveness and cost data.

In the model, the effectiveness of the subject intervention and comparator in the clinical improvement of depressed individuals was compared (section 2.2.1.). This primary effectiveness endpoint was drawn from the results of the EVIDENT randomized controlled trial (14):

- **Patients with a clinical important improvement**, defined as five-point reduction on the Patient Health Questionnaire-9 (PHQ-9), for the cost-effectiveness analysis (CEA)

Additionally, and since depression is an illness characterized by its high relapse rate, the model considered a relapse probability (section 2.2.2). The structure, health states and health-state transitions of the model are shown in Figure 1.

Figure 1 Markov model structure



2.2. Health state transition probabilities

2.2.1. Clinically important improvement

The **Patients with a clinical important improvement endpoint** was measured at three months and at six months respectively. The relative risks of Deprexis® and CAU vs CAU are 0.569 and 0.677 for three and six months respectively (14). The calculation of the transition probabilities for the CAU intervention were straightforward, 0.202 (102 clinically improved individuals out of 504 patients) at three months and an additional 0.065 (26 clinically improved individuals out of the remaining 402 patients) at month six. On the other hand, for the Deprexis® intervention, these probabilities were multiplied by the following relative effectiveness: 1.757 at three months and 1.478 at six months. Additionally, the relative effectiveness between month 3 and month 6 was assumed to be the same for the following two cycles in the time horizon. This resulted in the following transition probabilities:

- Probability of a clinically important PHQ-9 improvement at month 3 with CAU per cycle=0.202
- Probability of a clinically important PHQ-9 improvement at month 6 (and on) with CAU per cycle=0.065
- Probability of a clinically important PHQ-9 improvement at month 3 with Deprexis® per cycle= 0.356

- Probability of a clinically important PHQ-9 improvement at month 6 (and on) with Deprexis® per cycle=0.095

2.2.2. Relapse probability

In a guidance document published by the health department of the Generalitat de Catalunya, it is stated that the probability of someone who has suffered a depressive episode of relapsing or having a recurrent disorder is high: 0.5 within the next two years (9). This two-year probability corresponds to an annual recurrence rate of 0.34657 and a 0.0625 probability of relapse per cycle. The same relapse probability was used for both Deprexis and CAU, assuming a worst-case scenario for Deprexis® to avoid amplifying its efficacy, therefore, sensitizing the model.

2.2.3. Death

The weighted, by sex and age, probability of death of the general population in Catalonia was estimated with data from the Catalonian Institute of statistics, and was equal to 0.00057144 per cycle for individuals aged 18 to 65 (15). The probability of death per cycle for patients with a clinically important improvement was assumed to be that of the general population. In a network meta-analysis study, a relative risk of mortality of 1.52 for depressed individuals was found (16), when applied, the resulting probability of death per cycle for depressed individuals was 0.000868592.

2.2.4. Transition matrixes

The resulting transition matrices for the Markov model are shown in Table 1.

Table 1 Transition matrixes for the Markov model

Transition matrix for Deprexis® and CAU			
3 months	**Persistent depression symptoms**	**Clinically important improvement**	**Death**
Persistent depression symptoms	0.6435	0.3556	0.0009
Clinically important improvement	0.0830	0.9369	0.0006
Death	0	0	1
Transition matrix for Deprexis® and CAU			
6 months	**Persistent depression symptoms**	**Clinically important improvement**	**Death**
Persistent depression symptoms	0.9036	0.0956	0.0006
Clinically important improvement	0.0830	0.9164	0.0009

Death	0	0	1
Transition matrix for CAU			
3 months	**Persistent depression symptoms**	**Clinically important improvement**	**Death**
Persistent depression symptoms	0.7968	0.2024	0.0009
Clinically important improvement	0.0830	0.9369	0.0006
Death	0	0	1
Transition matrix for CAU			
6 months	**Persistent depression symptoms**	**Clinically important improvement**	**Death**
Persistent depression symptoms	0.9345	0.0647	0.0009
Clinically important improvement	0.0830	0.9164	0.0006
Death	0	0	1

2.3. Calculation of the quality adjusted life-years

In order to obtain the **quality adjusted life-years (QALY)** for the cost-utility analysis (CUA), a conversion scale published by Furukawa et al. 2020 was used. The paper describes that a five-point improvement in PHQ-9 corresponded approximately with an increase in EQ-5D-3L (EuroQol 5 dimensions three levels) score by 0.03 and a ten-point improvement by approximately 0.25 (17). The utility used for depressed patients was obtained from a Study on the Costs and Burden of Depression in Catalonia and was equal to 0.864 (12). Therefore, the utility of a clinically improved individual was considered to be equal to 0.894 with the corresponding 0.03 improvement.

2.4. Costs

The cost of Deprexis® is 297.5 € (7) for every three-month cycle.

With regards to the cost of depression, in a publication from 2021 by Vieta et al., the direct and indirect costs of depression in Spain are compiled (18). This allowed to draw a clear distinction between the costs assumed for the analysis from the perspective of the NHS (direct costs) and from that of society (direct and indirect costs). A detailed description of the costs found in this publication can be seen in Table 2.

Table 2 Direct and indirect costs of depression in Spain

Direct costs	
Component	**Cost**
Primary care visits	183.00 €
Hospital emergency room visits	15.00 €
Specialist visits	40.50 €
Hospital stays	130.60 €
Laboratory tests	24.50 €
Conventional radiology	6.00 €
Axial tomography	0.60 €
Magnetic nuclear resonance	1.70 €
Other complementary tests	27.20 €
Electroconvulsive therapy	9.50 €
Anti-depressant medication	155.80 €
Total direct costs	**594.20 €**
Indirect costs	
Component	**Cost**
Temporary disability (days of occupational disability)	582.30 €
Permanent disability	2,058.80 €
Total indirect costs	**2,641.10 €**
Direct and indirect costs	
Total direct and indirect costs	**3,235.30 €**

The annual costs described in Table 2 were adapted for 3-month cycles, and assumed as the costs that patients with persistent depression symptoms incur, resulting in the following costs per cycle:

- Direct cost (NHS's perspective) of a patient with persistent depression symptoms: 148.60 €
- Direct and indirect (Society's perspective) cost of a patient with persistent depression symptoms: 808.83 €

In a study on the Social and Economic Burden of Mood Disorders and in the study on the Costs and Burden of Depression in Catalonia, it is explained that patients achieving remission of depression had total costs approximately one-third as great as those with persistent depression (12,19). Therefore, it was assumed that patients with a clinically important improvement had the following costs per cycle:

- Direct cost (NHS's perspective) per patient with a clinically important improvement: 49.53 €

- Direct and indirect (Society's perspective) cost of a patient with a clinically important improvement: 269.61 €

Additionally, in the study on the Costs and Burden of Depression in Catalonia, the indirect (Society's perspective) cost of premature death is described by age and sex (12). A weighted, by age and sex, cost of premature death was calculated and adapted for 3-month cycles, resulting in 524.74 €.

2.5. Base case, deterministic, and univariate one-way sensitivity analysis (OWSA) results calculation

The base case, deterministic results were expressed as follows for both, the NHS (direct costs) and Society's (direct and indirect costs) perspective as follows:

- Incremental cost-effectiveness ratio of Deprexis® and CAU vs. CAU

$$ICER = \frac{Cost\ of\ Deprexis - Cost\ of\ CAU}{Effectiveness\ of\ Deprexis - Effectiveness\ of\ CAU}$$

Where effectiveness is measured in terms of clinically improved individuals.

- Incremental cost-utility ratio of Deprexis® and CAU vs. CAU

$$ICUR = \frac{Cost\ of\ Deprexis - Cost\ of\ CAU}{QALY\ of\ Deprexis - QALY\ of\ CAU}$$

Additionally, a univariate one-way sensitivity analysis (OWSA) was performed to evaluate and identify the variables that have the greatest effect on the outcomes (ICER and ICUR) of the study. The OWSA was performed manually for an assumed standard error (SE) of 20% on the variables described in Table 3. Also, the Markov model was run for a period of 5 years to evaluate the sensitivity of the model to the ***Time Horizon*** variable. Finally, the minimum value for the utility variables was a 20% reduction to the base case and the maximum value was equal to 1 (not greater than a life year).

Table 3 Model input variables analyzed in the sensitivity analysis

Variable	Description	Base case	Range for the sensitivity analysis
CDep_direct	Direct cost of depressed patients	148.60 €	SE=20%
CDep_direct_indirect	Direct and indirect cost of depressed patients	808.83 €	SE=20%
CDeprexis	Cost of Deprexis	297.50 €	SE=20%

CImp_direct	Direct cost of clinically improved patients	49.53 €	SE=20%
CImp_direct_indirect	Direct and indirect cost of clinically improved patietns	269.61 €	SE=20%
Cpremature_deat	Societal cost of premature death	524.74 €	SE=20%
Discount rate	Yearly discount rate	3%	SE=20%
PImproveCAU_3	Probability of a clinically important PHQ-9 improvement at month 3 with CAU per cycle	0.2023810	SE=20%
PImproveCAU_6	Probability of a clinically important PHQ-9 improvement at month 6 with CAU per cycle	0.0646766	SE=20%
PImproveDeprexis_3	Probability of a clinically important PHQ-9 improvement at month 3 with Deprexis® per cycle	0.3555992	SE=20%
PImproveDeprexis_6	Probability of a clinically important PHQ-9 improvement at month 6 with Deprexis® per cycle	0.0955616	SE=20%
PMortDep	Mortality of depressed individuals per cycle	0.0008686	SE=20%
PMortGen	Mortality of the general population in Catalonia (ages 18 to 65) per Cycle	0.0005714	SE=20%
PRelapse	Probability of relapse per cycle	0.0829960	SE=20%
Time Horizon	Time Horizon	1 year	Markov model run until year 5
UDep	Utility of depressed individuals	0.864	Minimum value: Base case minus 20% Maximum value: 1
UImpr	Utility of clinically improved individuals	0.894	Minimum value: Base case minus 20% Maximum value: 1

3. Results

3.1. Base case deterministic results

The base case results from the perspective of the NHS reveled that the introduction of Deprexis® incurred an ICER of 3,866 € per clinically improved individual over the one-year time horizon and a ICUR of 125,498 € per QALY. For the analysis from the perspective of society, the results where 2,248 € per clinically improved individual over the one-year time horizon and 72,970 € per QALY respectively (Table 4).

Table 4 Base case results of the analysis – one year time horizon

Perspective	ICER	ICUR
National Health Service (direct costs)	3,866 € per clinically improved individual	125,498 € per QALY
Society (direct and indirect costs)	2,248 € per clinically improved individual	72,970 € per QALY

3.2. One-way sensitivity analysis results

In the OWSA, it was found that ***Time Horizon*** was the variable that had the most influence in the outcome of the CEA for both perspectives, when run for five years, the ICER increased by 19,141 € and 10,794 € per clinically improved individual from the perspective of the NHS and society respectively. In Figure 2 and Figure 3 the tornado diagrams for the CEA from both perspectives is shown.

Figure 2 Tornado diagram for the Incremental direct cost per clinically improved individual per year

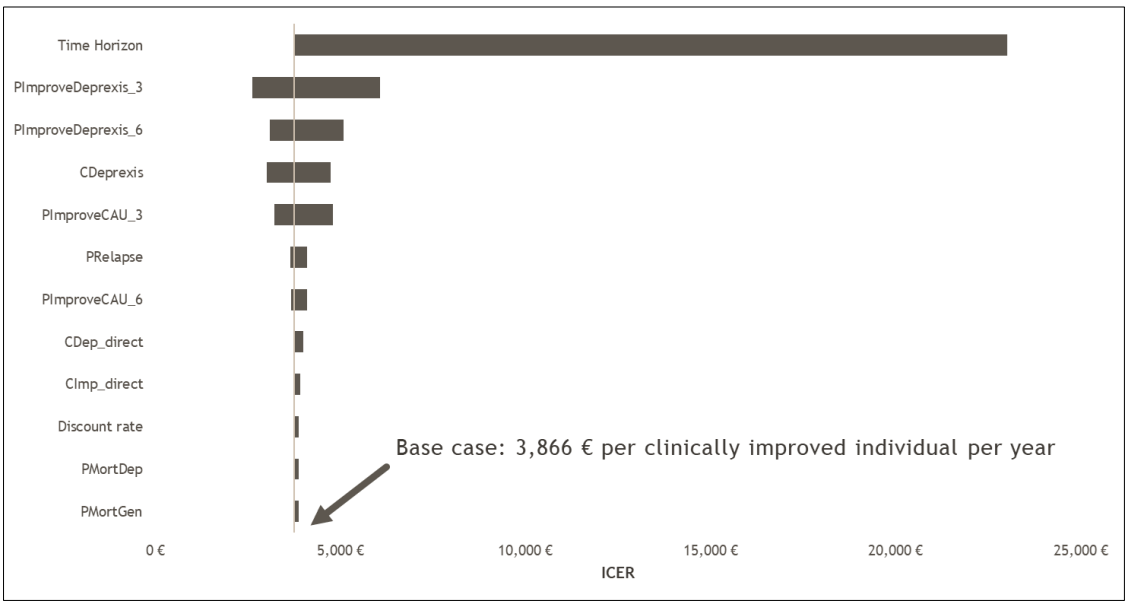
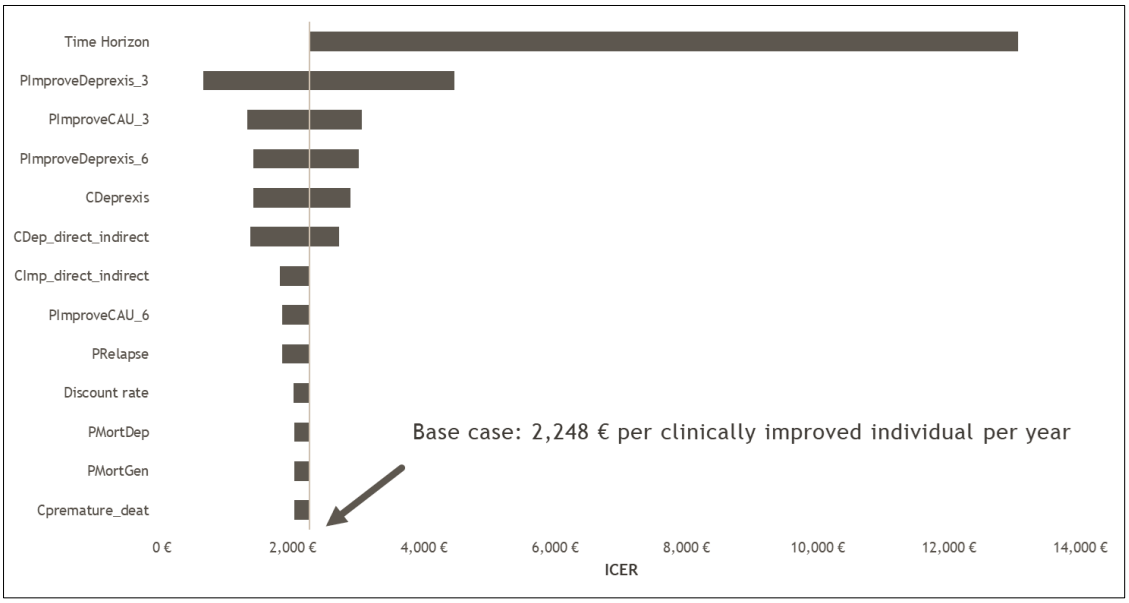


Figure 3 Tornado diagram for the Incremental direct and indirect cost per clinically improved individual per year



For the CUA, the variability was much higher than that of the CEA, as seen in Figure 4 and Figure 5. In these analyses, the variable that incurred the largest influence on the outcome was the ***Utility of Clinically Improved Individuals***, with a variability on the ICUR of 4,762,929 € and 2,490,837 € per QALY from the perspective of the NHS and society respectively. As with the CEA, the ***Time horizon*** variable also had a strong influence on the ICUR found in the CUA,

this increase was of 516,069 € and 290,707 € per QALY from the perspective of the NHS and society respectively.

Figure 4 Tornado diagram for the Incremental direct cost per QALY

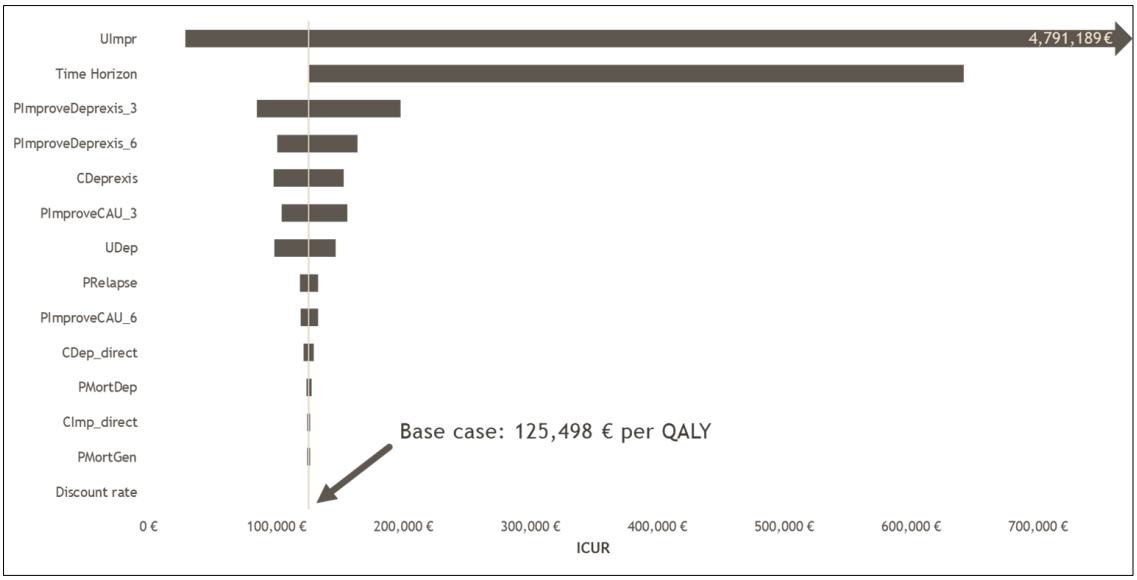
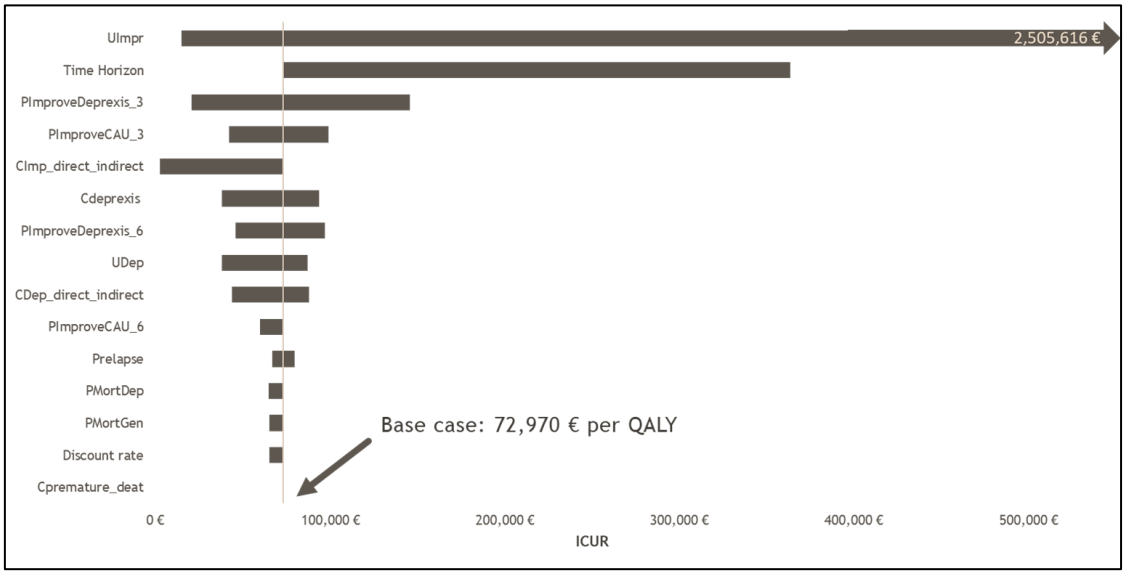


Figure 5 Tornado diagram for the Incremental direct and indirect cost per QALY



4. Discussion

In the region of Catalonia there is no official willingness-to pay threshold with regards to the clinical improvement per depressed individual nor for gained QALY. In the clinical study considered for this analysis, Deprexis® was studied as a complement of CAU, particularly for

CBT, however, the clinical development of Deprexis® also included studies in which it compared as a partial replacement of CBT or versus the CBT waiting list (7).

Psychotherapy, by which CBT is delivered, has a direct cost of approximately 75 € per hour of session in Catalonia (12) and the waiting lists for it tend to be long. In Spain, there are only 20 psychologist per 100,000 inhabitants which translates into waiting periods that can range from 26 to over 70 days and, in many cases, results in the patient opting for private practice (increased societal cost) (11). Taking into account the cost and the reduced access to CBT, the introduction of Deprexis® as a partial replacement of psychotherapy or as a tool prescribed during the waiting period, could result in an ICER far below the one found in this analysis.

From the OWSA, the Time horizon variable was the variable with the largest influence on the resulting ICER and the second largest on the ICUR. This is mainly due to the fact that the greatest effectiveness of Deprexis® was at three months and this effectiveness reduce at 6 months and forward.

The greatest limitation of this study was that, in the utility conversion scale, an individual transformation could not be done, resulting in an ICUR that surpasses the threshold of even the most expensive health interventions (over 50,000€ per QALY for orphan drugs)(20). For the conversion factor between PHQ-9 to QALY utilities, all patients were given the minimum utility improvement, 0.03 for a 5-point improvement on the PHQ-9 scale regardless of their real improvement. The conversion factor escalates to up to a 0.25 utility gained for a ten-point improvement in the PHQ-9 scale, however, the absence of data on the individual improvement did not allow to consider any improvement beyond a 5-point reduction on the PHQ-9 scale (17).

5. Conclusion

The CEA of the introduction of Deprexis® as a complement of CAU resulted in a ICER of 3,866 € and 2,248 € per clinically improved individual over the one-year time horizon from the perspectives of the NHS and society, respectively. This analysis was performed solely on the effectiveness of Deprexis® as a complement of CAU and not as a partial replacement of CBT or as a tool prescribed during the waiting list period, scenarios for which the resulting ICER could be expected to be far below the one found in this analysis. With regards to the CUA, the results were not favorable for Deprexis® due to the absence of individual data on the improvement of the patients on the PHQ-9 scale, therefore a concise conclusion cannot be drawn.

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